

Supplementary Information

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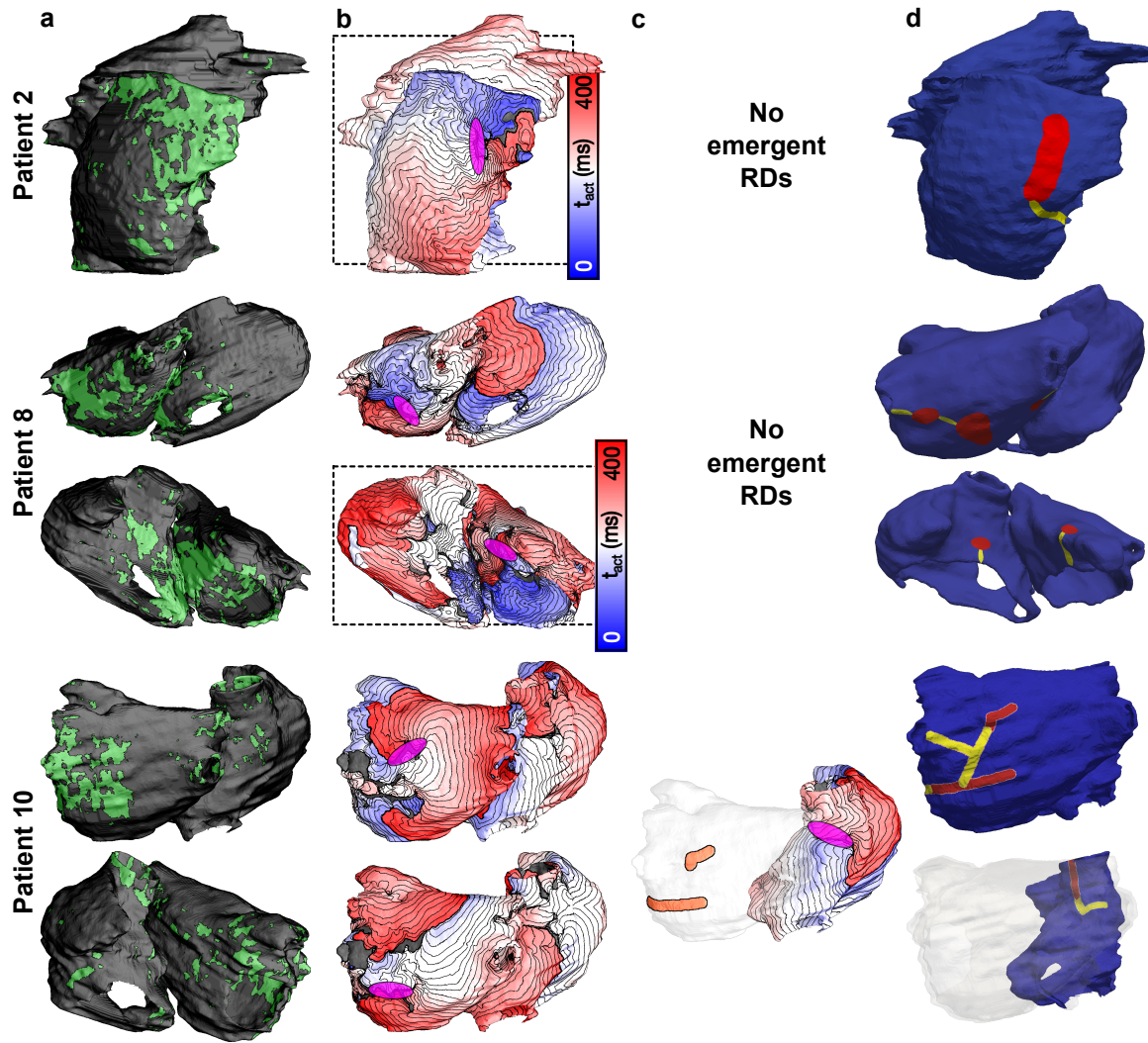


Fig. S1 | Examples of the process to determine the OPTIMA ablation targets for three additional patients. All legends are identical to those used in **Fig. 2** in the main text unless otherwise noted. **a**, Three patient-specific atrial models as reconstructed from segmented LGE-MRI scans, including the distribution of fibrotic tissue. For patient 2, only the right atrial (RA) posterior view is shown since that was the only location where an RD was observed in simulations; otherwise, the views shown are posterior (top) and anterior (bottom). **b**, Example activation sequences during arrhythmia morphologies induced following the rapid pacing protocol, and the corresponding persistent reentrant drivers (RDs, pink) obtained from the analysis of the induced arrhythmias. **c**, If applicable, activation sequences associated with arrhythmia emerging anew in the models following virtual ablation (lesions shown in orange), and the corresponding emergent RDs (pink); For Patient 10, the left atrial outline is shown in silhouette to facilitate visualization of an RD on the posterior aspect of the superior vena cava. **d**, Custom-tailored OPTIMA ablation treatment plans, including targets corresponding to all RDs (pre-ablation and emergent) and lesion lines connecting the latter to non-conductive tissue boundaries.

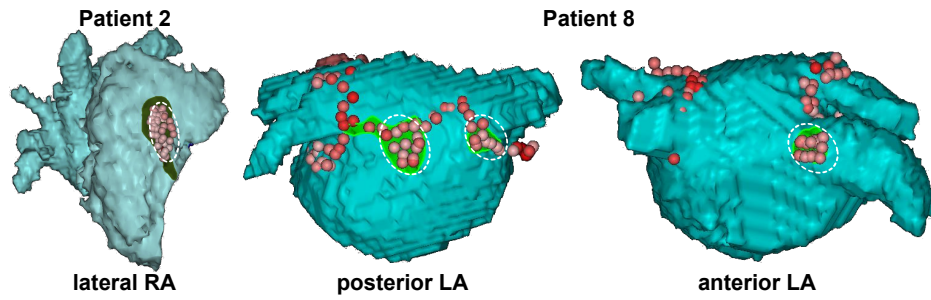


Fig. S2 | Locations of clinical ablation lesions from OPTIMA-guided procedure in two of the patients from Fig. S1. Ablation catheter tip locations are marked as red dots in the left and right atria (LA/RA) as rendered in the CARTO intracardiac mapping system at the end of the clinical ablation procedure. Dashed ellipses indicate locations ablated based on sites of persistent RDS as identified by OPTIMA; connecting-line ablation lesions were also executed.

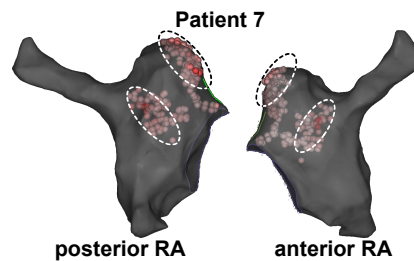


Fig. S3 | Locations of clinical ablation lesions from OPTIMA-guided procedure in patient 7. See also middle panels of Fig. 3a in main text. Ablation catheter tip locations are marked as red dots in the right atrium (RA) as rendered in the CARTO intracardiac mapping system at the end of the clinical ablation procedure. Dashed ellipses indicate locations ablated based on the sites of persistent RDS as identified by OPTIMA (two distinct locations in the posterior RA, viewed from both sides of the atrial geometry).

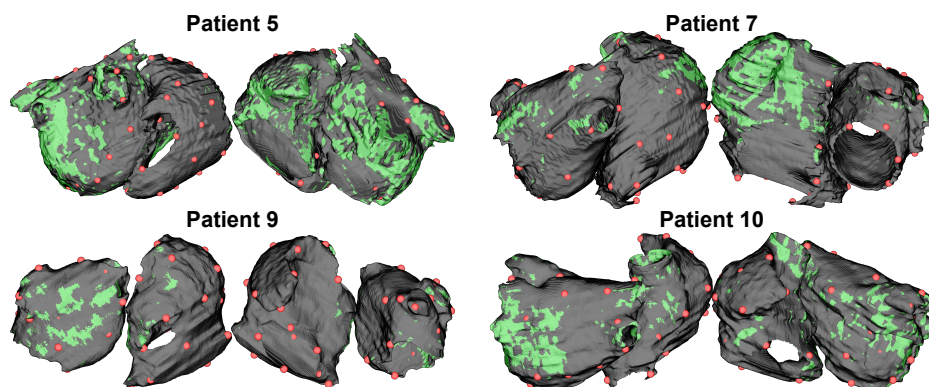


Fig. S4 | Illustration of the sites from which rapid pacing was performed (red) in four patient-specific atrial models to elicit arrhythmias. The distribution of fibrotic (green) and non-fibrotic (grey) tissue in both atria was reconstructed from the patient's LGE-MRI scan.

Table S2 | Detail regarding OPTIMA-derived RDs and their locations in all 10 patients. Values in the n_{PS} column indicate the number of pacing sites from which each RD was induced. RDs marked with * are those that emerged after virtual ablation. LA/RA = left/right atrium; LAA/RAA = left/right atrial appendage; LSPV/LIPV/RSPV/RIPV = left/right superior/inferior pulmonary vein; SVC/IVC = superior/inferior vena cava; TV = tricuspid valve; MV = mitral valve.

ID	LA	RA	Description	n_{PS}	Ablated?
1		x	Lateral RA, near TV	4	Yes
	x		Posterior LA, near LPVs	1	Yes
	x		Posterior LA, inferior to LIPV	1	Yes
	x		Posterior LA, near RIPV	1	Yes
	x		Anterior LA, inferior to LSPV	1	Yes
2		x	Posterior/Lateral RA	4	Yes
3	x		Septal LA, near RSPV	9	Yes
	x		Posterior LA, near RIPV	3	Yes
	x		Posterior LA, near LIPV	2	Yes
		x	Posterior RA	2	Yes
	x		Postero-inferior LA	1	Yes
	x		Anterior LA, behind RSPV	1	Yes
5	x*		Directly beneath LPVs	8	Yes
	x		Between MV and LPVs	4	Yes
	x		Postero-inferior LA	3	Yes
	x*		Superior cusp of LSPV	3	Yes
	x		Posterior LA, near LPVs	2	Yes
	x		Anterior LA	1	Yes
	x		Anterior LA, near RSPV	1	Yes
	x		Inferior cusp of LSPV	1	Yes
	x*		Directly beneath RPs	1	Yes
		x*	Anterior RA, beneath SVC	1	No
		x*	Anterior RA, near TV	1	No
6	x		Anterior LA, inferior to RSPV	7	Yes
	x		Posterior LA, near LIPV	6	Yes
		x	Lateral RA	1	No
7		x*	Posterior RA	14	Yes
		x	Anterior RA, near TV	6	Yes
		x	Lateral RA, near TV	6	Yes
	x		Near base of LAA	4	Yes
		x	Posterior base of RAA	3	Yes
	x*		Posterior LA, near base of LAA	3	Yes
8	x		Posterior LA, between RIPV/MV	12	Yes
		x	Anterior RA, below SVC	5	No
	x		Anterior LA, in inter-atrial groove	5	No
	x		Posterior LA, near LIPV	2	Yes
	x		Posterior LA, below RPs	1	Yes
	x		Anterior LA, near base of LAA	1	Yes
9	x		Posterior LA, between LIPV/RIPV	9	Yes
	x		Posterior LA, inferior to LIPV	8	Yes
10	x		Posterior LA, near LPVs	7	Yes
	x		Inferior to LAA base, above MV	5	Yes
		x*	Anterior RA, near SVC	5	No
	x		Posterior LA, near LIPV	1	Yes

Table S3 | Clinical outcomes for OPTIMA-guided ablation procedures. FU = follow-up; PAF = paroxysmal atrial fibrillation; SR = sinus rhythm; Afl = atrial flutter.

ID	Rhythm at end of FU	FU duration (days)	Atrial ablation during FU
1	SR	543	No
2	SR	347	No
3	PAF/Afl	417	PAF/Afl
5	SR	399	No
6	SR	302	No
7	SR	315	No
8	SR	264	No
9	SR	239	No
10	SR	197	No

Movie S1 | Dynamic illustration of all steps in the OPTIMA approach. Results and analysis shown are for Patient 10 (see also lower two rows of **Fig. S1**). All legends are identical to those used in **Fig. 2** and **Fig. S1**, including: bi-atrial fibrosis distribution, rapid pacing site locations (as in **Fig. S4**), spatiotemporal renderings of membrane voltage (V_m), activation time (t_{act}) sequences, virtual ablation lesions, and personalized OPTIMA treatment plans consisting of reentrant driver (RD) locations and connecting lines.

Movie S2 | Dynamic illustration of results shown in the top two rows of Fig. 2 (Patient 5). First, a rotating view of the patient-specific atrial model is presented. Next, spatiotemporal renderings of membrane voltage (V_m) in the pre-ablation model representing induced reentrant drivers (RD1 and RD2) in the postero-inferior left atrium (LA) and the LA posterior wall, respectively. Third, emergent RDs (emRD1 and emRD2) observed in the post-ablation model are shown in the left then right pulmonary vein carina regions. Finally, a rotating view of the custom-tailored OPTIMA ablation treatment plans is shown, including targets corresponding to all RDs (pre-ablation and emergent) and lesion lines connecting the latter to non-conductive tissue boundaries. All legends are identical to those in **Fig. 2**.

Movie S3 | Same as Movie S2 but for results shown in the third and fourth rows of Fig. 2 (Patient 7). RD1 location: anterior aspect of left atrial appendage (LAA); RD2 location: lateral wall of right atrium (RA); emRD1 location: posterior aspect of LAA; emRD2 location: lateral RA, superior to RD1. RD = reentrant driver.

Movie S4 | Same as Movie S2 but for results shown in the bottom two rows of Fig. 2 (Patient 9). Since no reentrant drivers (RDs) were observed in the pre-ablation model, two episodes of macro-reentrant atrial tachycardia/flutter (AT/Afl) around the mitral valve annulus are shown (first counter-clockwise, then clockwise). emRD1 location: posterior left atrium (LA), below the left inferior pulmonary vein; emRD2 location: posterior LA, below the right inferior pulmonary vein.